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Munich, 15th June 2000
On behalf of the President of the German Patent and Trade Mark Office

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Seiler

Sustained-release, oral pharmaceutical forms of administration

The present invention relates to at least partially sustained-release, oral pharmaceutical forms of administration in which the pharmaceutical active substance, tramadol, is present at least partially as a compound formed in situ which has a water solubility of ≤50 mg/ml, and to processes for their preparation.

The administration of pharmacological active substances in the form of sustained-release preparations represents a therapeutic improvement for many of these active substances, especially analgesics. Even for pharmacological active substances with a relatively short half-life in the organism, retardation makes it possible to provide a preparation with a long-lasting action and also, through more constant blood levels, to avoid side effects and improve the patients' observance of the dosage instructions.

Pharmacological active substances can be retarded e.g. by being embedded in a sustained-release matrix or by the application of sustained-release film coatings.
The retardation of very readily water-soluble active substances, e.g. tramadol hydrochloride, an analgesic for controlling intense to very intense pain, with the aid of film coatings is often expensive because film coatings for such active substances frequently constitute an inadequate diffusion barrier or the permeability of these film coatings changes during storage (P.B. O'Donnell, J.W.

McGinity, "Mechanical Properties of Polymeric Films, Prepared from Aqueous Polymeric Dispersions in Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms", Drugs and the Pharmaceutical Science, vol. 79, ed. J.W. McGinity, Marcel Decker, New York, Basle, Hong Kong 1997).

The manufacture of preparations with sustained-release film coatings applied from aqueous dispersion therefore requires expensive coating processes with multilayer films or time-consuming tempering processes, as described in US-PS 5,645,858, US-PS 5,580,578, US-PS 5,681,585 or US-PS 5,472,712, in K. Bauer, "Coated Pharmaceutical Dosage Forms", Medpharm Scientific Publishers, Stuttgart 1998, B. Sutter, Thesis, University of Düsseldorf, 1987, or in F.N. Christensen, Proceed. Intern. Symp. Contr. Rel. Bioact. Mater. 17, 124, 1990.

It is also possible to retard pharmaceutical active substances by reducing their solubility, e.g. by forming sparingly soluble salts (H. Sucker, Pharmazeutische Technologie (Pharmaceutical Technology), Georg Thieme Verlag, Stuttgart, New York 1991). In some cases, however, the use of such sparingly soluble salts in forms of administration requires very expensive processes to prepare these salts.

The object of the present invention was therefore to provide forms of administration which do not exhibit the disadvantages of the state of the art.

Surprisingly, it has now been found that this object is achieved by the preparation of at least partially sustained-release, oral pharmaceutical forms of administration in which the active substance tramadol is present at least partially as a compound formed in situ which has a water solubility of ≤50 mg/ml.

The water solubility of the compound formed in situ is preferably ≤20 mg/ml and particularly preferably ≤5 mg/ml.

To prepare the compound formed in situ, the active substance tramadol, preferably as a water-soluble salt and particularly preferably as tramadol hydrochloride, is reacted with a water-soluble, pharmaceutically acceptable salt of another, acidic pharmaceutical active substance or auxiliary substance which forms with tramadol a compound with a water solubility of ≤50 mg/ml, preferably ≤20 mg/ml and particularly preferably ≤5 mg/ml. These compounds are classified as sparingly water-soluble compounds.

In terms of the invention, in situ formation means that the tramadol is mixed with another, acidic pharmaceutical active substance or auxiliary substance or water-soluble salts thereof, preferably during the preparation of the forms of administration according to the invention, moistened and optionally extruded or formulated under some other energy input.

The sodium salt of diclofenac, ibuprofen, naproxen, acetylsalicylic acid, salicylic acid, benzoic acid, saccharin, cyclamate or acesulfame is preferably used as

the water-soluble salt of the other, acidic pharmaceutical active substance and/or biocompatible auxiliary substance for the preparation of the tramadol compound formed in situ.

The sustained-release, oral pharmaceutical forms of administration according to the invention can contain the tramadol component and the other pharmaceutical active substance and/or auxiliary substance in any molar ratio.

In one preferred embodiment of the forms of administration according to the invention, the tramadol component is in excess and is therefore released therefrom at different rates. This means that, as well as the retarded release of tramadol, part of the active substance is released rapidly as an initial dose.

In another preferred embodiment of the forms of administration according to the invention, the tramadol component and the other, acidic pharmaceutical active substance or auxiliary substance are in equimolar amounts as the sparingly soluble compound formed in situ. Thus, the two active substances or the active substance/ auxiliary substance undergo retarded release at the same rate.

In one particularly preferred embodiment of the forms of administration according to the invention, tramadol hydrochloride and diclofenac sodium have been reacted in situ to give a very sparingly soluble compound with a water solubility of ≤0.3 mg/ml. The proportions of

tramadol hydrochloride to diclofenac Na in such forms of administration according to the invention are preferably 0.5:1 to 4:1 and particularly preferably 1:1 to 2:1. Tramadol is preferably used in excess for the in situ reaction with diclofenac so that, in such forms of administration, an initial dose of tramadol is released rapidly and tramadol and diclofenac undergo retarded release at the same rate. A rapid alleviation of pain can be achieved by the combination containing the active substance released immediately as an initial dose. The slow release of the active substances from the sustained-release form then enables the analgesic action to be maintained over a longer period.

Other preferred sustained-release forms of administration according to the invention contain the compound, formed in situ, of the active substances tramadol and diclofenac from equimolar amounts so that the total amount of each active substance undergoes retarded release at the same rate.

The at least partially sustained-release, oral pharmaceutical forms of administration according to the invention are preferably multiparticulate formulations, particularly preferably in the form of granules, microparticles, microtablets or pellets and very particularly preferably in the form of pellets, optionally filled into capsules. The pellets are preferably produced by extrusion and spheronization and preferably have a diameter of 0.1 to 3 mm.

The forms of administration according to the invention can also be formulated as coated tablets or ordinary tablets, preferably as rapidly disintegrating tablets. The tablets can be compressed from pellets which particularly preferably are of the rapidly disintegrating type.

One particular advantage of the forms of administration according to the invention is that the tramadol is retarded by the formation of a compound with other active substances and/or auxiliary substances, said compound having a water solubility of ≤50 mg/ml, without the use of a sustained-release matrix and/or a sustained-release coating.

The pharmaceutical forms of administration according to the invention preferably have at least one enteric coating which dissolves as a function of pH. Because of this coating, said forms pass through the stomach undissolved and the active substance(s) and/or auxiliary substance(s) only undergoes (undergo) controlled release in the intestinal tract. The enteric coating can be applied from aqueous solution or dispersion and/or from organic solution. It preferably dissolves at a pH of between 5 and 7.

The enteric coating preferably consists of shellac, polymethacrylic acid/ethyl acrylate or polymethacrylic acid/methyl acrylate/methyl methacrylate copolymer, polymethacrylic acid/methyl methacrylate copolymers, hydroxypropyl methyl cellulose acetate-succinate, cellulose acetate-phthalate, polyvinyl acetate-phthalate,

hydroxypropyl methyl cellulose phthalate and/or cellulose acetate-trimellitate.

A retardation over and above that achieved by the in situ formation of the compound, and hence a further modification of the release of the active substance tramadol and optionally other active substances, can be effected by the various methods known to those skilled in the art.

Preferably, a further retardation can be effected with the aid of sustained-release coatings. Suitable sustained-release coatings include water-insoluble waxes or polymers, e.g. acrylic resins, preferably poly(meth)acrylates, or water-insoluble celluloses, preferably ethyl cellulose. These materials are known from the state of the art, e.g. Bauer, Lehmann, Osterwald, Rothgang, "Überzogene Arzneiformen" ("Coated Pharmaceutical Forms"), Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, 1988, p. 69 et seq., which is introduced here by way of reference and thus forms part of the disclosure.

To adjust the rate of release of the active substances, the sustained-release coatings can optionally contain, in addition to the water-insoluble polymers, non-retarding, preferably water-soluble polymers in amounts of up to 30 wt.%, such as polyvinylpyrrolidone or water-soluble celluloses, preferably hydroxypropyl methyl cellulose or hydroxypropyl cellulose, and/or hydrophilic pore-forming

agents such as sucrose, sodium chloride or mannitol, and/or the known plasticizers.

To further retard the release of the sparingly soluble tramadol compound, the forms of administration according to the invention can preferably also contain said compound in a sustained-release matrix, preferably as a uniform distribution.

Matrix materials which can be used are physiologically compatible, hydrophilic materials known to those skilled in the art. The hydrophilic matrix materials used are preferably polymers and particularly preferably cellulose ethers, cellulose esters and/or acrylic resins. The matrix materials used are very particularly preferably ethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, hydroxymethyl cellulose, poly(meth)acrylic acid and/or derivatives thereof such as their salts, amides or esters.

Other preferred matrix materials are those consisting of hydrophobic materials such as hydrophobic polymers, waxes, fats, long-chain fatty acids, fatty alcohols or corresponding esters or ethers, or mixtures thereof. The hydrophobic materials used are particularly preferably C_{12}-C_{30} fatty acid mono- or diglycerides and/or C_{12}-C_{30} fatty alcohols and/or waxes, or mixtures thereof.

The sustained-release matrix material used can also be mixtures of said hydrophilic and hydrophobic materials. The release of the active substances will preferably be

adjusted so that the forms of administration according to the invention have to be taken at most twice a day and particularly preferably only once a day. With their knowledge of the action of analgesics, those skilled in the art are aware of the doses in which they are to be used in order to achieve the desired effect.

Another possible way of modifying the release of the active substance tramadol and optionally other active substances from the forms of administration according to the invention is by varying their surface area and/or by using hydrophilic auxiliary substances. The effect of enlarging the surface area, e.g. by using smaller pellets, is to increase the rate of release of the active substances. The result of increasing the amount of hydrophilic auxiliary substances, e.g. lactose, in the pellet core is again to increase the rate of release of the active substance(s).

The forms of administration according to the invention preferably have an analgesic action and/or an action on urinary incontinence, particularly preferably an analgesic action.

The invention also provides processes for the preparation of the at least partially sustained-release, oral pharmaceutical forms of administration according to the invention, wherein tramadol and another, acidic pharmaceutical active substance or auxiliary substance or water-soluble salts thereof, and optionally other

auxiliary substances, are mixed, moistened and formulated under an energy input.

The mixture is preferably moistened with aqueous media and particularly preferably with water or aqueous binder solutions.

The energy input preferably takes the form of pressure and/or heat.

In one preferred embodiment of the process according to the invention, the mixture is moistened, optionally granulated several more times, extruded at least once and optionally converted to the final formulation. Preferably, the mixture is moistened, optionally extruded several times and pelleted and/or dried, optionally mixed with other auxiliary substances and compressed to tablets. The pellets are preferably provided with an enteric coating before being compressed.

In one particularly preferred embodiment of the process according to the invention, tramadol hydrochloride and diclofenac sodium are used to prepare the compound formed in situ.

If the forms of administration according to the invention are converted to the final formulation, this can be carried out by the various methods known to those skilled in the art.

Depending on the embodiment, the forms of administration according to the invention can also contain, as additional constituents, the conventional auxiliary substances and additives known to those skilled in the art. If the forms of administration according to the invention have coatings, these can be applied by conventional processes, e.g. by the coating pan process, by the spraying of solutions, dispersions or suspensions, by the hot-melt process or by the powder application process.

Surprisingly, a feature of the forms of administration according to the invention is that the release of the active substance tramadol and optionally other active substances from the forms of administration according to the invention is not affected by varying the release conditions within the conventional framework, for example by means of the ion concentration of the buffers, the presence of surface-active substances, the use of different types of buffer and/or the application of different mechanical stresses. Even after prolonged storage at an elevated temperature of up to 40°C, the rates of release of the active substance(s) from the forms of administration according to the invention do not change.

This release of the active substances from the at least partially sustained-release, oral pharmaceutical forms of administration according to the invention follows kinetics which otherwise can only be achieved by expensive matrix systems. Surprisingly, it is found that the release of the pharmaceutical active substances can be retarded without using other sustained-release systems, so the

release profiles can be modelled by varying the size of the pharmaceutical form and incorporating soluble auxiliary substances, while maintaining the common rate of release of the two active substances. Surprisingly, despite the very small particle size averaging ≤5 µm, this release of the two active substances from the sparingly soluble tramadol/diclofenac compounds prepared in situ takes place with exactly the same retardation as the release of separately prepared salts of tramadol and diclofenac from identical forms of administration, albeit having substantially larger particle sizes of approx. 20 - 100 µm.

As the release of the active substance tramadol and optionally other active substances from the forms of administration according to the invention can be retarded without using additional sustained-release systems, said forms of administration can be produced in less time and at less expense.

The invention is illustrated below with the aid of the Examples. The illustrations are given solely by way of example and do not limit the general spirit of the invention.

The release profile of the preparations of the Examples was determined as follows:

The preparations were tested either in a spinning cage apparatus (Examples 1 to 6) or in a paddle stirrer (Example 7), as described in the European Pharmacopoeia, at a temperature of 37°C (±0.5°C) and a speed of rotation of 100 min^{-1} or 50 min^{-1}. In Example 1, the preparation was tested for ten hours, in Example 6 for five hours and in Example 5 for four hours in 900 ml of artificial intestinal juice without enzymes (pH 7.2). In Examples 2 to 4 and 7, the preparation was tested first for two hours in 600 ml of artificial gastric juice without enzymes (pH 1.2) and then for a further eight hours in 900 ml of artificial intestinal juice without enzymes (pH 7.2).

The amount of active substances released at any given time was determined by HPLC. The values and curves shown have been averaged over 3 samples in each case.

Examples:

Example 1:

125 g of tramadol hydrochloride, 125 g of diclofenac sodium and 250 g of microcrystalline cellulose (Avicel PH 101, FMC) were homogeneously mixed in a Kenwood Chef mixer for 10 minutes and then granulated with water in an amount sufficient for moistening. The sticky lumpy mass of granules was then extruded in a Nica extruder (type E140) with a 1.0 mm extrusion die. While the rods of extrudate were initially still extremely sticky, they changed in the course of the extrusion process to a very dry extrudate with insufficient plasticity for subsequent spheronization. The extrudate was moistened and granulated again. The resulting granules were extruded again in the Nica extruder and the moist extrudate was then converted to round pellets of uniform size in a Nica spheronizer (type S450). The pellets were dried in a drying cabinet at a temperature of approx. 50°C and fractionated into sieve fractions, ≥90% of the pellets falling within the desired sieve class of 800 - 1250 µm.

Composition of the pellets:

Tramadol-HCl	50 mg
Diclofenac-Na	50 mg
Microcrystalline cellulose (Avicel PH 101, FMC)	100 mg
	200 mg

The release profile was as follows:

Time in min	Amount in mg released from 200 mg of pellets	
	for tramadol	for diclofenac
30	10	7
120	18	15
300	26	24
600	35	33

Example 2:

200 g of tramadol hydrochloride, 100 g of diclofenac sodium, 22 g of powdered succinic acid and 332 g of microcrystalline cellulose (Avicel PH 101, FMC) were homogeneously mixed in a Kenwood Chef mixer for 10 minutes and processed to pellets analogously to Example 1.

Composition of the pellets:

Tramadol hydrochloride	100 mg
Diclofenac sodium	50 mg
Succinic acid, powdered	11 mg
Microcrystalline cellulose (Avicel PH 101, FMC)	166 mg
	327 mg

500 g of the classified pellets were then provided with an enteric coating in a fluidized bed at an air inlet temperature of 40°C with an aqueous shellac solution, the

amount of shellac applied being 5 wt.%, based on the weight of the pellets.

Film coating for 500 g of pellets:

Aqueous shellac solution ASL 125 (20% solids content, Marchand & Cie)	125 g
Triethyl citrate	1.25 g
Water	136.25 g

The release profile was as follows:

Time in min	Amount in mg released from 344 mg of pellets	
	for tramadol	for diclofenac
120	0	0
240	61	10
480	76	25
600	84	28

Example 3:

1.25 kg of tramadol hydrochloride, 1,25 kg of diclofenac sodium, 1.0 kg of lactose monohydrate, 0.75 kg of microcrystalline cellulose (Avicel PH 101, FMC) and 0.75 kg of colloidal microcrystalline cellulose (Avicel RC 591, FMC) were mixed in a Diosna (type P25) and granulated. The pellets were produced analogously to Example 1 with the following changes. The sticky moist granules were not extruded after granulation, but spread directly onto metal trays sealed with foil and heated for

20 minutes in a drying cabinet at 50 to 70°C, thereby avoiding moisture losses. The granules were then moistened and granulated again. They are extruded in a Nica type (E140 extruder) with a 0.8 mm extrusion die. The extrudate was spheronized in a Nica spheronizer (type S450). After the pellets had been dried in a drying cabinet, they were classified, between ≥90% of the pellets falling in the desired sieve class of between 0.63 and 1.0 mm.

Composition of the pellets:

Tramadol hydrochloride	75 mg
Diclofenac sodium	75 mg
Lactose monohydrate	60 mg
Microcrystalline cellulose (Avicel PH 101, FMC)	45 mg
Colloidal microcrystalline cellulose (Avicel RC 591, FMC)	45 mg
	300 mg

5 kg of the pellets were then coated in a Hüttlin spherical coater at an air inlet temperature of 40°C with 21% wt.% of Eudragit L-55, based on the total weight of the pellets, from an aqueous dispersion of the following composition:

Film coating for 5 kg of pellets:

Eudragit L30D-55 (Röhm, 30% aqueous dispersion of 1:1 polymethacrylic acid/ethyl acrylate

copolymer)	3500 g
Eudragit NE30D (Röhm, 30% aqueous dispersion of polyethyl acrylate/methyl methacrylate copolymer)	315 g
Triethyl citrate	175 g
Talcum, micronized	262.5 g
Water	3657.5 g

Composition of the capsules:

400 mg of the coated pellets, together with 46 mg of tramadol initial-dose pellets (corresponding to 25 mg of tramadol hydrochloride, 10.5 mg of Avicel PH 105 and 10.5 mg of I-HPC LH31), were filled into size 0 hard gelatin capsules on a Zanasi E6 encapsulating machine with 2 pellet dispensing stations.

The release profile was as follows:

Time in min	Amount in mg released per capsule	
	for tramadol (100 mg dose)	for diclofenac (75 mg dose)
30	25	0
120	28	0
240	56	29
480	79	50
600	85	56

Example 4:

1.5 kg of tramadol hydrochloride, 1.0 kg of diclofenac sodium, 1.0 kg of lactose monohydrate, 0.75 kg of microcrystalline cellulose (Avicel PH 101, FMC) and 0.75 kg of colloidal microcrystalline cellulose (Avicel RC 591, FMC) were mixed in a Diosna (type P25) and granulated. The pellets were produced analogously to Example 3 with the following changes. The reaction of the diclofenac sodium with the tramadol hydrochloride took place directly after the first granulation, in the mixer, by heating the jacket to a temperature of 70°C for 30 min, the stirrer blade being switched on for a few brief periods. After the reaction, the second granulation was carried out directly without emptying.

Composition of the pellets:

Tramadol hydrochloride	75 mg
Diclofenac sodium	50 mg
Lactose monohydrate	50 mg
Microcrystalline cellulose (Avicel PH 101, FMC)	37.5 mg
Colloidal microcrystalline cellulose (Avicel RC 591, FMC)	37.5 mg
	250 mg

5 kg of pellets were then coated in a Hüttlin spherical coater at an air inlet temperature of 40°C with 22 wt.% of Eudragit L-55, based on the total weight of the pellets, from an aqueous dispersion of the following composition:

Film coating for 5 kg of pellets:

Eudragit L30D-55 (Röhm, 30% aqueous dispersion of 1:1 polymethacrylic acid/ethyl acrylate copolymer)	3667 g
Triethyl citrate	220 g
Talcum, micronized	550 g
Water	4913.5 g

Composition of the capsules:

348 mg of the coated pellets, together with 46 mg of tramadol initial-dose pellets (corresponding to 25 mg of tramadol hydrochloride, 10.5 mg of Avicel PH 105 and 10.5 mg of I-HPC LH31), were filled into size 0 hard gelatin capsules on a Zanasi E6 encapsulating machine with 2 pellet dispensing stations.

The release profile was as follows:

Time in min	Amount in mg released per capsule	
	for tramadol (100 mg dose)	for diclofenac (50 mg dose)
30	27	0
120	32	0
240	78	24
480	94	40
600	99	45

Example 5:

100 g of tramadol hydrochloride, 69 g of saccharin sodium and 169 g of microcrystalline cellulose (Avicel PH 101, FMC) were homogeneously mixed in a Kenwood Chef mixer for 10 minutes and then processed to pellets analogously to Example 1.

Composition of the pellets:

Tramadol hydrochloride	100 mg
Saccharin sodium	69 mg
Microcrystalline cellulose (Avicel PH 101, FMC)	169 mg
	338 mg

The release profile was as follows:

Time in min	Proportion released in % for tramadol
30	84
120	100
240	104

Example 6:

100 g of tramadol hydrochloride, 84 g of naproxen sodium and 184 g of microcrystalline cellulose (Avicel PH 101, FMC) were homogeneously mixed in a Kenwood Chef mixer for 10 minutes and then processed to pellets analogously to Example 1.

Composition of the pellets:

Tramadol hydrochloride	100 mg
Naproxen sodium	84 mg
Microcrystalline cellulose (Avicel PH 101, FMC)	184 mg
	368 mg

The release profile was as follows:

Time in min	Proportion released in %	
	for tramadol	for naproxen
30	72	55
120	91	88
240	101	100
300	102	102

Example 7:

1.5 kg of tramadol hydrochloride, 1.0 kg of diclofenac sodium, 1.0 kg of lactose monohydrate, 0.75 kg of microcrystalline cellulose (Avicel PH 101, FMC) and 0.75 kg of colloidal microcrystalline cellulose (Avicel RC 591, FMC) were homogeneously mixed in a Diosna (type P25) for 10 minutes and processed to pellets analogously to Example 3.

Composition of the pellets:

Tramadol hydrochloride	75 mg
Diclofenac sodium	50 mg
Lactose monohydrate	50 mg
Microcrystalline cellulose (Avicel PH 101, FMC)	37.5 mg
Colloidal microcrystalline cellulose (Avicel RC 591, FMC)	37.5 mg
	250 mg

5 kg of pellets were then coated in a Hüttlin spherical coater at an air inlet temperature of 40°C with 21 wt.% of Eudragit L-55, based on the total weight of the pellets, of the following composition from an aqueous dispersion:

Film coating for 5 kg of pellets:

Eudragit L30D-55 (Röhm, 30% aqueous dispersion of 1:1 polymethacrylic acid/ethyl acrylate copolymer)	3500 g
Eudragit FS 30D (Röhm, 30% aqueous dispersion of polymethacrylic acid/methyl acrylate/methyl methacrylate copolymer)	350 g
Triethyl citrate	210 g
Glycerol monostearate (Cutina GMS, Henkel)	92.4 g
Water	3134.6 g

322.5 mg of pellets, corresponding to a dose of 75 mg of tramadol hydrochloride and 50 mg of diclofenac sodium,

were subsequently mixed first with 22.5 mg of crosslinked polyvinylpyrrolidone (Kollidon CL, BASF) and then with 205.6 mg of Cellactose (Meggle), 25 mg of tramadol hydrochloride and 1.4 mg of magnesium stearate and compressed to 7 x 14 mm notched oblong tablets weighing 577 mg. These disintegrate back to the individual pellets in an aqueous medium.

The release profile was as follows:

Time in min	Amount in mg released per tablet	
	for tramadol (100 mg dose)	for diclofenac (50 mg dose)
30	25	0
120	25	0
240	65	22
360	77	31
420	81	35
600	91	42

Claims:

1. At least partially sustained-release, oral pharmaceutical forms of administration, characterized in that their pharmaceutical active substance, tramadol, is present at least partially as a compound formed in situ which has a water solubility of ≤50 mg/ml.

2. Forms of administration according to Claim 1, characterized in that the water solubility is ≤20 mg/ml and preferably ≤5 mg/ml.

3. Forms of administration according to Claim 1 or 2, characterized in that the tramadol has been used as a water-soluble salt, preferably as tramadol hydrochloride, to prepare the compound formed in situ.

4. Forms of administration according to one or more of Claims 1 to 3, characterized in that the tramadol component has been reacted with a water-soluble, pharmaceutically acceptable salt of another, acidic pharmaceutical active substance or auxiliary substance to prepare the compound formed in situ.

5. Forms of administration according to Claim 4, characterized in that the salt which has been used is the sodium salt of diclofenac, ibuprofen, naproxen, acetylsalicylic acid, salicylic acid, benzoic acid, saccharin, cyclamate or acesulfame.

6. Forms of administration according to one or more of Claims 1 to 5, characterized in that the tramadol component is present in excess.

7. Forms of administration according to Claim 6, characterized in that the tramadol is released at different rates.

8. Forms of administration according to one of Claims 1 to 5, characterized in that the tramadol and the acidic pharmaceutical active substance or auxiliary substance are present in equimolar amounts as a compound formed in situ.

9. Forms of administration according to Claim 8, characterized in that the tramadol and the acidic active substance or auxiliary substance are released at the same rate.

10. Forms of administration according to one or more of Claims 4 to 9, characterized in that tramadol hydrochloride and diclofenac sodium have been used as the active substances.

11. Forms of administration according to Claim 10, characterized in that the molar ratio of tramadol to diclofenac is 0.5:1 to 4:1 and preferably 1:1 to 2:1.

12. Forms of administration according to Claim 10 or 11, characterized in that at least part of the tramadol

and at least part of the diclofenac are released at the same rate.

13. Forms of administration according to Claim 10, characterized in that the tramadol and the diclofenac are present in equimolar amounts as a compound formed in situ and are each released at the same rate.

14. Forms of administration according to one or more of Claims 1 to 13, characterized in that they are multiparticulate formulations, preferably in the form of granules, microparticles, microtablets or pellets and particularly preferably in the form of pellets, optionally filled into capsules.

15. Forms of administration according to one or more of Claims 1 to 13, characterized in that they are formulated as coated tablets or ordinary tablets, preferably as rapidly disintegrating tablets and particularly preferably as tablets compressed from pellets.

16. Forms of administration according to one or more of Claims 1 to 15, characterized in that they have at least one enteric coating.

17. Forms of administration according to one or more of Claims 1 to 16 with an analgesic action.

18. Process for the preparation of at least partially sustained-release, oral forms of administration

according to one of Claims 1 to 17, characterized in that tramadol and an acidic pharmaceutical active substance or auxiliary substance or water-soluble salts thereof, and optionally auxiliary substances, are mixed, moistened and formulated under an energy input.

19. Process according to Claim 18, characterized in that the mixture is moistened with aqueous media, preferably water or aqueous binder solutions.

20. Process according to Claim 18 or 19, characterized in that the energy input takes the form of pressure and/or heat.

21. Process according to one of Claims 18 to 20, characterized in that the mixture is moistened, optionally granulated several more times, extruded at least once and optionally converted to the final formulation.

22. Process according to one of Claims 18 to 21, characterized in that the mixture is moistened and optionally extruded several times and/or dried, optionally mixed with other auxiliary substances, pelleted and optionally compressed to tablets.

23. Process according to Claim 22, characterized in that the pellets are provided with at least one enteric coating before being compressed.

24. Process according to one or more of Claims 18 to 23, characterized in that tramadol hydrochloride is reacted as the tramadol salt and diclofenac sodium is reacted as the other active substance.

Abstract:

The present invention relates to at least partially sustained-release, oral pharmaceutical forms of administration in which the pharmaceutical active substance, tramadol, is present at least partially as a compound formed in situ which has a water solubility of ≤50 mg/ml, and to processes for their preparation.